Secondary Metabolites by Chemical Screening, 3 [1] Side-Chain Modification of Elaiophylin

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Base catalyzed deglycosidation of elaiophylin leads to a reactive enone system. Following addition of thiols yield side-chain modified products of the title compound.

Elaiophylin (**1**) is a macrodiolide antibiotic which was first isolated from *Streptomyces melanosporus* [2]. First it was attempted to elucidate the structure by an alkaline degradation of **1** [3–7]. Under acidic conditions the cleavage of the carbohydrate units was achieved [6]. The modification of the side-chain by glycosidation or even acylation was not possible because of steric hindrance of OH-13 [8].

During our work on structure modification of elaiophylin (**1**) we found reaction conditions for a controlled alkaline deglycosidation. Reaction of **1** with KHCO_3 in water/ethanol/ethyl acetate leads to a β -elimination with L-deoxyfucose as leaving group. The corresponding monoenone **2** was obtained in 34% and the dienone **3** in 52% yield. The *trans*-stereochemistry of the 12-double bond was confirmed by the coupling constant $J_{12,13} = 15.9$ Hz in the ^1H NMR spectrum. Obviously, the elimination is faster than the retro-aldol cleavage under these conditions. The *trans*-configuration of the double bond indicates that the hemiacetale is opened prior to elimination of L-deoxyfucose. The base attack at C-12, instead of deprotonation at OH-9, which would be the first step of the retro-aldol cleavage, can be explained by steric hindrance through hydrogen bonding of OH-9 to the carbonyl group at C-1'.

In the ^{13}C NMR spectra of **3** only 21 signals were observed because of the C_2 -symmetry. Compound **2** in contrast exhibited 48 signals because of its unsymmetry. Hereby 27 signals of **1** and 21 signals of **3** could be detected in the ^{13}C NMR spectra of **2**.

The hydration of **2** and **3** with Pd/H_2 results in the formation of 13,13'-dideoxyoctahydroelaiophylin (**4**) and the corresponding unsymmetric product **5** in 92% and 85% yield, respectively.

phylidene (**5**) and the corresponding unsymmetric product **4** in 92% and 85% yield, respectively.

Addition of thiols to the enone-system in **5** offers the possibility to synthesize modified side-chains in elaiophylidene for the first time. When **5** was refluxed with ethanethiol or mercaptoethanol in THF in the presence of triethylamine as catalyst, **6** and **7** were obtained in 82% and 74% yield. The β -stereochemistry of the thio-groups at C-13 was based on the coupling constants of $\text{H}_{\text{ax}}\text{-13}$ in the ^1H NMR spectra. For example with **6** the pseudo sextett of H-13 could be explained by $J_{\text{Hax-12 Hax-13}} = 12.5$ Hz, $J_{\text{Hax-14 Hax-13}} = 12.5$ Hz and $J_{\text{Heq-12 Hax-13}} = 3.6$ Hz.

Table I. ^{13}C NMR data of elaiophylin derivatives (chemical shifts in ppm in pyridine- d_5 at 75.5 MHz).

	3	5	6	7
1	168.0	174.7	168.5	168.5
2	122.1	34.4	122.1	122.0
3	145.3	24.8*	145.4	145.3
4	131.4	24.5*	131.5	131.5
5	145.0	32.8	145.0	145.0
6	42.2	34.0	42.0	41.9
7	76.8	77.1	77.0	76.9
8	37.6	42.9	37.3	37.3
9	72.2	70.5	70.8	70.8
10	46.7	38.4	43.2	43.1
11	202.7	98.3	99.2	99.1
12	131.6	33.3	42.7	42.9
13	148.3	24.6	41.2	41.6
14	52.8	43.9	47.8	47.9
15	68.9	70.0	68.3	68.3
16	22.1	20.0	20.1	20.0
17	15.7	16.1	15.7	15.6
18	10.1	9.4	9.8	9.7
19	9.1	7.3	7.5	7.4
20	24.3	24.8*	21.3	21.3
21	12.2	10.9	9.7	9.6
1'			23.9	15.3
2'			32.9	62.4

* These signals may be interchanged.

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The alkaline deglycosidation of the macrolide elaiophylin **1** is a convenient method to produce valuable intermediates on preparative scale allowing further modification.

Experimental

Melting points were determined with a Reichert hot stage microscope and are not corrected. NMR spectra were recorded on a Bruker AM 300 with TMS as internal standard. FAB-mass spectra were taken by a Kratos MS 50 with 3-nitrobenzyl-alcohol as matrix. Optical rotation was measured with a Perkin Elmer spectrometer 241.

Deglycosidation to **2** and **3**

10 g (9.8 mmol) **1** was refluxed in a mixture containing 150 ml of water, 50 ml of ethanol and

70 ml of ethyl acetate with 25 g of potassium-hydrogencarbonate for 6 h. The organic solvents were evaporated and the water phase was extracted four times with ethyl acetate. The organic phase was evaporated and the residue chromatographed on silica gel using chloroform/methanol (40:1) as eluent; yield 2.9 g (34%) **2** and 3.7 g (52%) **3**.

2: $[\alpha]_{20}^{\text{D}} + 13^\circ$ ($c = 1$, CH_3OH), positive FAB-MS $m/z = 899$ (MNa^+ , 100%).

$\text{C}_{48}\text{H}_{76}\text{O}_{14}$ (877.1)
 Calcd C 65.7 H 8.7,
 Found C 65.0 H 8.5.

3: $[\alpha]_{20}^{\text{D}} + 107^\circ$ ($c = 1$, CH_3OH), positive FAB-MS $m/z = 751$ (MNa^+ , 100%), ^1H NMR (pyridine- d_5) $\delta = 0.8$ (t, 3H, $J = 7.4$ Hz, H-21), 1.0 (d, 3H, $J = 6.6$ Hz, H-17), 1.15 (d, 3H, $J = 6.9$ Hz, H-18), 1.23 (d, 3H, $J = 6.2$ Hz, H-16), 1.4 (d, 3H, $J = 6.9$ Hz, H-19), 1.6 (m, 1H, H-20), 1.75 (m, 1H, H-20), 2.1 (m, 1H, H-14), 2.3 (m, 1H, H-8), 2.6 (m, 1H, H-6), 3.35 (d, 1H, $J = 2.9$ Hz and $J = 6.9$ Hz, H-10), 4.07 (m, 1H, H-15), 4.32 (d, d, 1H, $J = 8.3$ Hz, $J = 2.0$ Hz, H-9), 5.65–5.85 (m, 3H, H-2, H-5, H-7), 6.15 (d, d, 1H, $J = 11.3$ Hz, $J = 15.3$ Hz, H-4), 6.4 (d, 1H, $J = 15.9$ Hz, H-12), 7.2 (m, 2H, H-3, H-13) ppm.

$\text{C}_{42}\text{H}_{64}\text{O}_{10}$ (728.9)
 Calcd C 69.2 H 8.9,
 Found C 69.0 H 8.3.

Hydrogenation to 4 and 5

1 g of **2** or **3** was dissolved in 50 ml of methanol and 400 mg of palladium on charcoal (Merck) was added. The hydrogenation was carried out at room temperature for 2 h. The reaction mixture was filtered and concentrated and the residue was chromatographed on silica gel with chloroform/methanol (40:1). The yield of **4** was 92% and that of **5** was 85%.

4: positive FAB-MS $m/z = 909$ (MNa^+).

$\text{C}_{48}\text{H}_{86}\text{O}_{14}$ (887.2)

Calcd C 65.0 H 9.8,

Found C 65.4 H 9.3.

5: $[\alpha]_{20}^D +26^\circ$ ($c = 1$, CHCl_3), m.p. 152–153 °C, positive FAB-MS $m/z = 763$ (MNa^+), ^1H NMR (pyridine- d_5) $\delta = 4.0$ (m, 1H, H-15), 4.5 (m, 1H, H-9), 5.6 (d, 1H, $J = 2.5$ Hz, H-7).

$\text{C}_{42}\text{H}_{76}\text{O}_{10}$ (741.1)

Calcd C 68.1 H 10.3,

Found C 67.6 H 10.0.

Addition of thiols to 6 and 7

1 g **3** was refluxed in a mixture containing 20 ml of THF, 1 ml of thiol and 0.5 ml of triethylamine for 6 h. The reaction mixture was concentrated and chromatographed on silica gel with chloro-

form/methanol (40:1). The yield of **6** was 82% and that of **7** was 74%.

6: positive FAB-MS $m/z = 874$ (MNa^+ , 100%), ^1H NMR (pyridine- d_5) $\delta = 2.6$ (m, 1H, H-6), 2.8 (d, d, $J = 12.8$ Hz and $J = 3.6$ Hz, 1H, H-12), 3.4 (pseudo sextett, 1H, $J = 12.5$ Hz and $J = 3.6$ Hz, H-13), 4.1 (t, $J = 14$ Hz, H-2'), 4.2 (m, 1H, H-15), 4.7 (d, d, $J = 5.2$ Hz, $J = 9.8$ Hz, H-9), 5.5–5.7 (m, 3H, H-2, H-5, H-7), 6.15 (d, d, 1H, $J = 11.3$ Hz, $J = 15.3$ Hz, H-4), 7.2 (m, 1H, H-3) ppm.

$\text{C}_{46}\text{H}_{76}\text{O}_{10}\text{S}_2$ (852.9)

Calcd C 64.8 H 9.0,

Found C 64.5 H 8.7.

7: positive FAB-MS $m/z = 907$ (MNa^+ , 100%), ^1H NMR (pyridine- d_5) $\delta = 2.55$ (m, 3H, H-6 and H-1'), 2.75 (d, d, 1H, $J = 12.8$ Hz, $J = 3.5$ Hz, H-12), 3.35 (pseudo sextett, $J = 12.5$ Hz and $J = 3.5$ Hz, 1H, H-13), 4.25 (m, 1H, H-15), 4.7 (m, 1H, H-9), 5.5–5.7 (m, 3H, H-2, H-5, H-7), 6.15 (d, d, 1H, $J = 15.3$ Hz, $J = 11$ Hz), 7.2 (m, 1H, H-3) ppm.

$\text{C}_{46}\text{H}_{76}\text{O}_{12}\text{S}_2$ (885.3)

Calcd C 62.4 H 8.7,

Found C 62.7 H 8.8.

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